

Extensively Drug-Resistant *Salmonella* Typhi Infections Among U.S. Residents Without International Travel



Distributed via the CDC Health Alert Network

February 12, 2021, 1:00 PM ET

CDCHAN-00439

Summary

The Centers for Disease Control and Prevention (CDC) is providing—

1. Information on extensively drug-resistant (XDR) *Salmonella* Typhi (Typhi) infections among U.S. residents without international travel, and
2. Treatment recommendations for XDR Typhi infection.

Background

Typhoid fever is a systemic illness caused by the bacterium *Salmonella enterica* serotype Typhi (Typhi). Most people in the United States diagnosed with typhoid fever acquired it during international travel, but some acquired it in the United States. The disease is treated with antibiotics; without appropriate antibiotic treatment, 12–30% of people with typhoid fever will die.

Typhi is transmitted through contaminated food and water and person-to-person contact. CDC recommends [vaccination](#) for people traveling to places where typhoid fever is common. Because typhoid fever vaccines are not 100% effective, travelers should always practice [safe eating and drinking habits](#) to help prevent infection.

In 2016, a large outbreak of extensively drug-resistant (XDR) Typhi infections began in Sindh province, Pakistan [1]. XDR Typhi strains are resistant to antibiotics generally recommended to treat typhoid fever, including ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, and trimethoprim-sulfamethoxazole. Isolates from patients linked to the outbreak in Pakistan are susceptible to carbapenems and azithromycin. Infections among travelers to or from Pakistan have been reported globally, including in the United States.

As of January 14, 2021, CDC has received 71 reports of XDR Typhi infection in the United States, with specimens obtained from February 9, 2018, through November 16, 2020. Among 67 patients with known travel history, 58 (87%) had traveled to Pakistan in the 30 days before illness began ([Figure](#)).

Nine (13%) patients from six states (NY [3], CA [2], IL, MD, NJ, and TX) reported that they had not traveled to Pakistan or any other country. Specimens from these nine patients were obtained from November 7, 2019, through October 7, 2020, with eight obtained in 2020. Susceptibility testing of these specimens showed the same resistance pattern described in Pakistan. CDC has not identified linkages among these patients or a common source of infection.

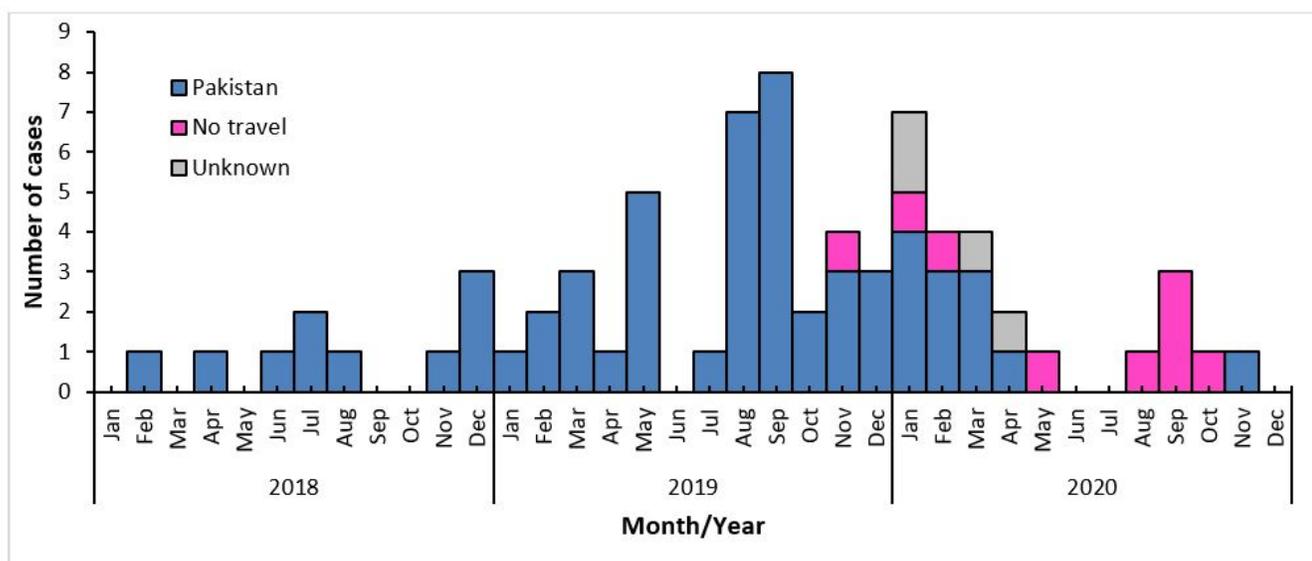
Case reporting of U.S. Typhi infections for 2020 is not yet complete. To date, 17 states have reported Typhi cases for 2020 compared with 39 states for 2019. Among 11 patients without international travel in 2020, eight patients were infected with XDR Typhi, one patient was infected with non-XDR Typhi, and susceptibility testing is pending for two others.

Before the outbreak in Pakistan, no case of ceftriaxone-resistant Typhi infection had been identified in the United States [2]. An unrelated cluster of ceftriaxone-resistant Typhi infections linked to Iraq has been reported in the United States and the United Kingdom [2].

Clinicians should consider empiric treatment with a carbapenem, azithromycin, or both agents for suspected typhoid fever in patients who did not travel out of the United States and for those who traveled to Pakistan or Iraq. Ceftriaxone remains an appropriate empiric treatment option for patients who traveled to countries other than Pakistan and Iraq. Clinicians should adjust treatment based on results of susceptibility testing.

This investigation is ongoing.

Figure. XDR Typhi cases by month of first positive culture and travel history — United States, 2018–2020 (n = 71)



Recommendations for Clinicians

- Consider that typhoid fever symptoms and clinical presentation may resemble those of other febrile infectious diseases.
 - Symptoms of typhoid fever include fever, headache, constipation or diarrhea, malaise, chills, and myalgias.
 - Severe or complicated typhoid fever can include bacteremia with sepsis or shock, gastrointestinal complications (e.g., intestinal perforation, peritonitis, intestinal hemorrhage, hepatitis), and neurologic complications (e.g., encephalopathy).
- Obtain a 30-day international travel history from all patients with suspected or confirmed typhoid fever.
 - Although most Typhi infections are acquired during international travel, Typhi can be acquired in the United States.

- Order blood cultures if typhoid fever is suspected; multiple cultures are usually needed.
 - Bone marrow cultures have the highest sensitivity and may be considered for some patients, such as those who have already started or completed a course of antimicrobial treatment.
 - Stool, urine, and duodenal cultures may also be helpful.
- Order antimicrobial susceptibility testing for Typhi isolates and adjust treatment accordingly.
- Consider the following in the selection of **empiric treatment** for patients with typhoid fever while awaiting susceptibility testing results and when the patient is not linked to a culture-confirmed case of typhoid fever with a known antimicrobial resistance profile.
 - *U.S. patients who did not travel outside the United States in the 30 days before illness began:* Patients might be infected with XDR Typhi. Consider prescribing a carbapenem (particularly if patients have severe or complicated illness) or azithromycin for empiric treatment.
 - *U.S. patients who traveled to Pakistan in the 30 days before illness began:* Most patients are infected with XDR Typhi [2]. Prescribe a carbapenem (particularly if patients have severe or complicated illness) or azithromycin for empiric treatment.
 - *U.S. patients who traveled to Iraq in the 30 days before illness began:* Most patients have strains that are resistant or have reduced susceptibility to ciprofloxacin; some strains are also resistant to ampicillin and ceftriaxone [2]. Consider prescribing a carbapenem (particularly if patients have severe or complicated illness) or azithromycin for empiric treatment.
 - *U.S. patients who traveled to countries other than Pakistan and Iraq in the 30 days before illness began:* Most patients have strains that are susceptible to ceftriaxone [2], which remains an appropriate empiric treatment option.
- Consider that resistance to meropenem (a carbapenem) or azithromycin has not been documented in Typhi isolated in the United States during the past five years.
 - About 80% of Typhi strains are resistant or have decreased susceptibility to ciprofloxacin [3].
- Treat patients with XDR Typhi infection with a carbapenem, azithromycin, or both.
 - Treat patients with severe or complicated illness with a carbapenem, such as meropenem. Case reports have suggested that patients who do not improve on a carbapenem alone may benefit from the addition of a second antibiotic, such as azithromycin [4–7].
 - Patients with uncomplicated illness may be treated with oral azithromycin alone.
- Vaccinate patients who are at high risk for typhoid fever, including those traveling to parts of the world where typhoid fever is common, those in close contact with a typhoid carrier, and those who might work with Typhi in a laboratory.
- Counsel travelers about safe eating and drinking practices and advise them that vaccination is not 100% effective. People can become infected with Typhi through contaminated food and water and through person-to-person contact.
- Follow local health department requirements for reporting typhoid fever, which is a nationally notifiable illness. Because of the risk of asymptomatic carriage after recovery, many health departments recommend follow-up testing to ensure microbiological cure before people in high-risk occupations, such as food handlers, daycare workers, and healthcare workers, return to work.

Recommendations for Health Departments

If your health department is notified about a case of typhoid fever in a patient who did not travel outside the United States in the 30 days before illness began, CDC recommends the following actions:

- Local health departments should notify their state health department and follow jurisdictionally required actions or protocols.

- State health departments should email CDC at entericfever@cdc.gov as soon as possible to obtain a focused questionnaire to interview the patient and to initiate expedited antimicrobial susceptibility testing of the associated isolate by providing the isolate ID.
- State health departments should contact the public health laboratory that will receive the associated isolate to ensure that whole genome sequencing of the isolate is performed.

Recommendations for Public Health Laboratories

- Public health laboratories should prioritize whole genome sequencing of Typhi isolates when resources allow, especially if the patient did not travel outside the United States in the 30 days before illness began.
- Questions about whole genome sequencing or antimicrobial susceptibility testing can be directed to entericbacteria@cdc.gov.

For More Information

- [More typhoid fever information for healthcare professionals](#)
- [Travel notice about XDR typhoid fever in Pakistan](#)
- [Information about typhoid vaccination](#)
- [Food and water safety tips for international travelers](#)

References

1. Klemm EJ, Shakoor S, Page AJ, et al. [Emergence of an Extensively Drug-Resistant *Salmonella* enterica Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins](#) [↗](#) . mBio. 2018 Feb 20; 9(1): e00105–18. doi: 10.1128/mBio.00105-18. PMID: 29463654.
2. François Watkins LK, Winstead A, Appiah GD, et al. [Update on Extensively Drug-Resistant *Salmonella* Serotype Typhi Infections Among Travelers to or from Pakistan and Report of Ceftriaxone-Resistant *Salmonella* Serotype Typhi Infections Among Travelers to Iraq – United States, 2018-2019](#). *MMWR Morb Mortal Wkly Rep*. 2020 May 22; 69(20): 618–622. doi: 10.15585/mmwr.mm6920a2. PMID: 32437343.
3. CDC. [National Antimicrobial Resistance Monitoring System \(NARMS\) Now: Human Data](#). Atlanta, Georgia: U.S. Department of Health and Human Services, CDC. 12/14/2020. <https://www.cdc.gov/narmsnow>. Accessed 12/15/2020.
4. Petrin CE, Steele RW, Margolis EA, et al. [Drug-Resistant *Salmonella* typhi in Pakistan](#) [↗](#) . *Clin Pediatr (Phila)*. 2020 Jan;59(1):31–33. doi: 10.1177/0009922819881203. Epub 2019 Oct 11. PMID: 31603009.
5. Liu PY, Wang KC, Hong YP, et al. [The first imported case of extensively drug-resistant *Salmonella* enterica serotype Typhi infection in Taiwan and the antimicrobial therapy](#) [↗](#) . *J Microbiol Immunol Infect*. 2020 Mar 25: S1684-1182(20)30077-3. doi: 10.1016/j.jmii.2020.03.017. Epub ahead of print. PMID: 32253142.
6. Godbole GS, Day MR, Murthy S, et al. [First Report of CTX-M-15 *Salmonella* Typhi From England](#) [↗](#) . *Clin Infect Dis*. 2018 Jun 1; 66(12): 1976–77. doi: 10.1093/cid/ciy032. PMID: 29471386.
7. López-Segura N, Corberó-Rivali C, Maldonado-Fernández MC, et al. [Imported extensively drug resistant typhoid fever in a child travelling to Spain from Pakistan](#) [↗](#) . *J Travel Med*. 2019 Dec 23; 26(8): taz066. doi: 10.1093/jtm/taz066. PMID: 31504718.

The Centers for Disease Control and Prevention (CDC) protects people's health and safety by preventing and controlling diseases and injuries; enhances health decisions by providing credible information on critical health issues; and promotes healthy living through strong partnerships with local, national and international organizations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

HAN Message Types

- **Health Alert:** Conveys the highest level of importance; warrants immediate action or attention.
- **Health Advisory:** Provides important information for a specific incident or situation; may not require immediate action.
- **Health Update:** Provides updated information regarding an incident or situation; unlikely to require immediate action.
- **Info Service:** Provides general information that is not necessarily considered to be of an emergent nature.

###

This message was distributed to state and local health officers, state and local epidemiologists, state and local laboratory directors, public information officers, HAN coordinators, and clinician organizations.

###

[Top of Page](#)

Additional Resources

- [HAN Archive By Year](#)
- [HAN Types](#)
- [Sign Up for HAN Email Updates](#)
- [HAN Jurisdictions](#)